

Editorial

5-Fluorouracil in colorectal cancer, a never ending story

5-Fluorouracil (FU) is one of the oldest chemotherapeutic agents still in use. It was first synthesized by C. Heidelberger [5] based on the rationale that tumors would preferentially use uracil which had been put forward by Rutmann [12]. The potential mechanisms of action were unknown at this time.

This drug has played an important role in the treatment of a variety of cancers and is the main stay of the treatment of colorectal cancer. Still after so many years of use, the best way to apply this drug is not clear. It may vary depending on the type of primary or even the individual tumor. FU may be given by bolus injection, i.e., 3-5 minutes, by short infusion over 30 minutes to several hours, by 24 hours to 48 hours infusion or by long term infusion over one to several weeks or months. For some of these applications, randomized studies have been performed indicating that long term continuous infusion of FU is superior to bolus injection in terms of response rate, but not in terms of survival. The assessment of these (and other) trials using a FU bolus treatment is compromised by the fact that many clinicians or nurses give FU by short term infusions claiming that it would be better tolerated. Although this has not been shown in a controlled study, it is likely that by extending the duration of FU application even to 15 or 30 minutes, one will reduce not only toxicity but also efficacy. This can be explained by a limited capacity of the 5-FU degrading enzyme dehydropyrimidin-dehydrogenase which can be rapidly saturated following a bolus injection allowing for more 5-FU to be anabolized or activated.

In the late 1970s and early 1980s the interest in FU has been sparked by the observation that its activity *in vitro* can be improved through biochemical modulation [3]. This has been made possible through the increasing knowledge of the mechanisms by which FU acts. A number of modulators have been introduced. Methotrexate (MTX) and folinic acid (FA) have been studied extensively as modulators. MTX/FU and FU/FA have only been compared in one large study [11] where MTX/FU was given at a reduced dose intensity compared to the original regimen [6] and hence was inferior. Many studies have been performed comparing MTX/FU or FU/FA with FU single agent [1, 2]. These studies provide evidence of a modulating effect of both agents with increased response rates if equimolar doses of FU are being used – at the expense of increased toxicity. Still, the responses are not long enough to profoundly influence the course of the disease. It is possible that in some patients the FU plus modulator responsive part of the tumor is eliminated leaving a

more aggressive rest that regrows even faster. The finding of significantly superior times to progression and no difference in overall survival would indicate so. Studies trying to compare equitoxic regimens of FU plus modulator failed to even see a significant advantage of FU modulation [1]. Thus, I would challenge the statement of the late C. Moertel in his review in *New England Journal of Medicine* [9] (my letter to the editor of *New England Journal of Medicine* criticising this statement of C. Moertel has been rejected).

In this issue of *Annals of Oncology*, Dufour et al. lay to rest yet another hope of FU modulation [4]. Although they show a small advantage of FU plus α -interferon (IFN) over FU in terms of response rate and event-free survival, they rightly point to the fact that the added toxicity and cost and the failure to demonstrate a survival benefit are not worthy of pursuing this approach. They cite several studies that have come to the same conclusion.

Thus, the once exciting story of FU plus α -IFN in colorectal cancer ends in a disappointment.

This story started with a response rate of 76% in 17 previously untreated patients [14]. It continued with thousands of patients being treated worldwide by oncologists who believed in the results. Now, it seems that many of these patients have suffered for nothing. This story of FU plus α -IFN should again teach us that phase II studies are unsuitable tools to reliably detect the true effect of a treatment: single institution phase II response rate 76%, multi-institution phase II response rate 42% [15], multi-institution phase III response rate 20% [4]. N. Kemeny recently has summarized some of the reasons for these discrepancies especially in colorectal cancer [7]. Wadlers first paper would have deserved to be published in the *Journal of Irreproducible Results*.

In essence, has there been any progress in the treatment of metastatic colorectal cancer?

The results of the combination of FU with MTX or FA has shifted the attention towards colorectal cancer in the medical community. Patients with this disease are now more likely to receive chemotherapy and benefit in terms of progression-free and overall survival as compared to no treatment [10, 13].

Is there any foreseeable future?

The often cited 'new drugs' do not appear to considerably improve the outcome of metastatic colorectal cancer. Most of the phase III studies now on the way intend to show equivalence rather than superiority compared to FU alone or FU/FA. It is time to realize that colorectal cancer is a heterogenous disease or else,

it is more than one disease. In the same way we are looking for hormonal receptors in breast cancer, we need to identify factors in colorectal cancer tissues which help us to predict treatment outcome like thymidylate synthase and p53 [8]. Only then, we can improve the treatment results in one subgroup and spare the other patients unnecessary side effects.

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